OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,031,393**
(22) 1990/12/03
(43) 1991/06/15
(45) 1998/12/15

(72) Conte, Ubaldo, IT
(72) La Manna, Aldo, IT
(72) Colombo, Paolo, IT
(73) Jagotec AG, CH

(51) Int.Cl.[6] A61K 9/24, A61K 31/55, A61K 31/275
(30) 1989/12/14 (22694) IT

(54) **COMPRIMES A LIBERATION PROGRESSIVE DE SUBSTANCES ACTIVES**

(54) **TABLETS WITH CONTROLLED-RATE RELEASE OF ACTIVE SUBSTANCES**

EP 0432607

(57) Comprimés à libération contrôlée de substances actives, comportant un noyau de forme géométrique définie contenant la substance active, des substances polymériques qui se gonflent au contact de liquides aqueux et des substances polymériques ayant des propriétés gélifiantes, et un support appliqué audit noyau pour en recouvrir partiellement la surface, le support étant composé de substances polymériques qui sont lentement solubles et/ou lentement gélifiables en liquides aqueux, en substances plastifiantes et, éventuellement, en substances jouant un rôle d'adjuvant.

(57) Tablets with controlled-rate release of the active substances, consisting of a core of defined geometrical form containing the active substance, polymer substances which swell on contact with aqueous liquids and polymer substances with gelling properties, and a support applied to said core to partly cover its surface, the support consisting of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and possibly substances with an adjuvant function.

TABLETS WITH CONTROLLED-RATE RELEASE OF ACTIVE SUBSTANCES

ABSTRACT OF THE DISCLOSURE

Tablets with controlled-rate release of the active substances, consisting of a core of defined geometrical form containing the active substance, polymer substances which swell on contact with aqueous liquids and polymer substances with gelling properties, and a support applied to said core to partly cover its surface, the support consisting of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and possibly substances with an adjuvant function.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Tablets with controlled-rate release of the active substances, consisting of:
a core of defined geometrical form containing the active substance, polymer substances which swell on contact with aqueous liquids, substances with gelling properties, and a support applied to said core partially covering its surface, wherein said support consists of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, and plasticizing substances, the amount of the polymer substances being 30-90% by wt. of the support composition and that of the plasticizing substances being 2-15% by wt.; wherein:
(a) said polymer materials which swell on contact with aqueous liquids are selected from crosslinked sodium carboxymethylcellulose, crosslinked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethyl starch, potassium methacrylate/divinylbenzene copolymer, polymethylmethacrylate, crosslinked polyvinylpyrrolidone, and high molecular weight polyvinylalcohols;
(b) said substances with gelling properties are selected from methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-

C

molecular weight polyvinylalcohols, polyoxyethylene-glycols, and non-crosslinked polyvinylpyrrolidone; or

(c) polymers possessing both swelling and gelling properties are used, selected from medium viscosity hydroxypropylmethylcellulose and medium viscosity polyvinylalcohols;

(d) said slowly soluble and/or slowly gellable substances are selected from hydroxypropylmethylcellulose having a molecular weight of between 4,000 and 2,000,000, high-molecular weight carboxyvinylpolymers, polyvinyl-alcohols, scleroglucans, acrylates, methacrylates, hydroxypropylcellulose, sodium carboxymethylcellulose and hydrophilic cellulose derivatives;

(e) the ratio of polymer substances with swelling properties to gellable polymer substances is between 1:9 and 9:1; and

(f) said support has a thickness of between 10 microns and 3-4 mm.

2. Tablets as defined in claim 1, wherein the support applied to said core further contains an adjuvant substance selected from binders, hydrophylic agents and hydrophobic agents.

C

3. Tablets as defined in claim 2, wherein the adjuvant substance used in the preparation of the support is a substance acting as a binder selected from polyvinylpyrrolidone, methylcellulose, ethylcellulose, gum arabic, alginic acid and its derivatives.

4. Tablets as defined in claim 2, wherein the adjuvant substance used in the preparation of the support is a substance acting as an hydrophilic agent selected from mannitol, lactose, starch and colloidal silica.

5. Tablets as defined in claim 2, wherein the adjuvant substance used in the preparation of the support is a substance acting as an hydrophobic agent selected from hydrogenated castor oil, magnesium stearate, fatty substances, waxes, and natural and synthetic glycerides.

6. Tablets as defined in any one of claims 1 to 5, wherein said plasticizing substances are chosen from the group consisting of polyoxyethyleneglycols, castor oil, hydrogenated castor oil, ethyl phthalate, butyl phthalate, and natural, synthetic and semisynthetic glycerides.

C

7. Tablets as defined in any one of claims 1 to 6, wherein the core further contains a substance with an adjuvant function, selected from mannitol, ethylcellulose, magnesium stearate, and colloidal silica.

8. A process for preparing tablets as defined in any one of claims 1 to 7, wherein said core is prepared by compressing a granular mixture of the relative substances to 1000-4000 kg/cm^2, and said support is applied to the core by applying a granular mixture of relative substances prepared by screening and mixing until an easily-flowable homogeneous mixture is obtained, to part of the core surface by compressing to 1000-4000 kg/cm^2.

C

TABLETS WITH CONTROLLED-RATE RELEASE OF ACTIVE SUBSTANCES

Prior art

The controlled-rate release of active substances contained in tablets has been the subject of numerous studies and proposals particularly in recent years.

Important technical progress, mainly of interest to the pharmaceutical sector, was achieved with the development of a type of tablet allowing the constant controlled-rate release in accordance with zero order kinetics of substances both soluble and little soluble in water or aqueous liquids, as described in US patent 4,839,177.

Said patent claims a tablet consisting of:

a) a core comprising an active substance and having a geometrically defined form;

b) an insoluble support applied to said core to partly cover its surface and characterised in that the said core contains, in mixture with the active substance, a polymer material undergoing a high degree of swelling after contact with water or aqueous liquids and a gellable polymer material, which polymer materials can be replaced by a single polymer material having swelling and gelling properties, together with other adjuvant substances able to give the mixture suitable characteristics for its compression and acceptance of water, said support consisting of a polymer material insoluble in aqueous liquids.

The examples and information given in said patent clearly indicate that the basic characteristic of the support applied to a part of said core is its insolubility in aqueous liquids.

The tablets of said patent have however the drawback of requiring the use of solutions of polymer materials in organic solvents for applying the support, these solutions being difficult to evaporate and possibly leaving solvent traces in the pharmaceutical form, and in addition the tablets cannot be produced by the methods, procedures and equipment normally used in the tablet production industry. In addition the rigid support can result in cracking and sometimes flaking before the active substance has been completely released.

Summary

We have now discovered a new type of tablet with constant controlled-rate release of active substances in accordance with zero order kinetics, which obviates the drawbacks of tablets of the known art.

The tablets according to the present invention consist of:

- a core of defined geometrical form containing the active substance, polymer substances which swell on contact with aqueous liquids, substances with gelling properties, and possibly other substances with an adjuvant function, and
- a support applied to said core to partly cover its surface,

and are characterised in that said support consists of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and possibly other substances with an adjuvant function, which plasticizing action can also be performed by said polymer substances.

These tablets can be produced industrially using the already used technology and methods, and in addition they have the advantage

that the support remains intact until the complete release of the active substance.

Detailed description of the invention

The characteristics and advantages of the tablets with constant controlled-rate release (zero order kinetics) of active substances according to the present invention will be more apparent during the course of the following detailed description.

Said tablets consist of:

- a core of defined geometrical form containing the active substance, polymer substances which swell on contact with aqueous liquids, substances with gelling properties, and possibly other materials with an adjuvant function, and
- a support applied to said core to partly cover its surface, and consisting of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and substances with an adjuvant function, which plasticizing action can also be performed by said polymer substances.

The core is obtained by compressing the mixture containing the active substance under a pressure of between 1000 and 4000 kg/cm^2 and therefore assumes a defined geometrical form which is generally the form of a cylindrical tablet with flat, convex or concave bases as shown for example in Figures 1 to 5 in which the dotted part represents the core and the hatched part represents the support.

The following substances are used to prepare the core:

As polymer materials which swell on contact with aqueous liquids, essentially insoluble polymers are used such as crosslinked sodium carboxymethylcellulose, crosslinked hydroxypropylcellulose, high

molecular weight hydroxypropylmethylcellulose, carboxymethyl starch, potassium methacrylate/divinylbenzene copolymer, polymethylmethacrylate, crosslinked polyvinylpyrrolidone, high molecular weight polyvinylalcohols etc. Gellable polymer materials include methylcellulose, carboxymethylcellulose, low molecular weight hydroxypropylmethylcellulose, low molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-crosslinked polyvinylpyrrolidone etc. Polymers which possess both swelling and gelling properties such as medium viscosity hydroxypropyl-methylcellulose and medium viscosity polyvinylalcohols can also be used. Adjuvant substances include mannitol, ethylcellulose, magnesium stearate, colloidal silica and others.

The ratio of polymer substances with swelling properties to gellable polymer substances is between 1:9 and 9:1. The active substance content in the core varies with the type of substance and can be from 1 to 95% by weight.

The support has a thickness of between 10 microns and 3-4 mm depending on the hydrophilic characteristics of the components, its task being to limit and define the direction of release of the active substance contained in the core.

In this respect, as the support is generally less hydrophilic than the core and does not contain active substance, the transfer of active substance can occur to a significant and immediate extent only from that portion of the core which is not covered by the support.

The following substances are used to prepare the support.

The polymer substances slowly soluble and/or slowly gellable in

aqueous liquids, these substances being used either alone or in mixture with each other, are chosen from the group consisting of hydroxypropylmethylcellulose having a molecular weight of between 4,000 and 2,000,000, high molecular weight carboxyvinylpolymers, polyvinylalcohols, scleroglucans, acrylates, methacrylates, hydroxypropylcellulose, sodiumcarboxymethylcellulose and hydrophilic cellulose derivatives.

These polymer substances represent a quantity of between 2 and 95 weight% and preferably between 30 and 90 weight% of the support composition.

The support formulation also includes substances able to provide elasticity, such as polyoxyethyleneglycols, castor oil, hydrogenated castor oil, ethyl phthalate, butyl phthalate, and natural, synthetic and semisynthetic glycerides.

These substances represent a quantity of between zero and 50 weight% and preferably between 2 and 15 weight% of the support composition.

This ensures correct release kinetics, determined by the fact that the support is sufficiently elastic to follow any change consequent on the hydration of the core without causing cracking or gaps which would result in total release of the active substance.

Finally, the support formulation includes adjuvant substances acting as binders such as polyvinylpyrrolidone, methylcellulose, ethylcellulose, gum arabic, alginic acid and its derivatives, adjuvants acting as hydrophilic agents such as mannitol, lactose, starch, colloidal silica, and adjuvants acting as hydrophobic agents such as hydrogenated castor oil, magnesium stearate, fatty

substances, waxes, and natural and synthetic glycerides.

These substances represent a quantity of between zero and 50 weight% and preferably between 0.5 and 35 weight% of the support composition.

By adding hydrophilic and hydrophobic agents the hydrophilic properties of the chosen support can be suitably regulated on the basis of the characteristics of the active substance and the desired release rate.

The material for the support is prepared by mixing the constituent substances, possibly wetting with a binding solution in accordance with the known art, then bringing the mixture to the dry granular state.

Said material is given the necessary characteristics by screening and mixing with other components until an easily flowable homogeneous mixture is obtained.

Said material is applied to the core as a surface layer using using presses.

The support can be applied to one or two bases of the core as shown in Figures 1 and 2 respectively, or can be applied to the entire core surface with the exception of one base as shown in Figure 3, or to the entire lateral surface with the exclusion of the two bases as shown in Figures 4 and 5. The support is applied using a pressure of between 1000 and 4000 kg/cm^2.

The following examples are given as non-limiting illustration of the invention.

EXAMPLE 1

a - Preparation of the core granulate

The following materials were used in the indicated quantities to prepare 100,000 cores:

Diltiazem (Fermion)	4.500 kg
Hydroxypropylmethylcellulose (Methocel® K 100 M-Colorcon)	3.500 kg
Mannitol (USP grade - Carlo Erba)	1.000 kg
Ethylcellulose	0.375 kg
Magnesium stearate	0.100 kg
Colloidal silica (Syloid® 244 - Grace)	0.100 kg
95° ethanol	7.500 litres

The diltiazem was mixed intimately with the mannitol and hydroxypropylcellulose in a suitable mixer. A solution of ethylcellulose in 95° ethanol was prepared separately and used to wet the previously formed powder mixture. The homogeneous mass obtained in this manner was forced through an 800 micron grid and then dried to obtain a granulate which was passed through a 420 micron grid. The granulate obtained was mixed with the magnesium stearate and the colloidal silica in a suitable mixer, to obtain the granulate A1, which was white in colour.

b - Preparation of the support granulate

For forming 200,000 supports a granulate of the following composition was prepared:

Hydroxypropylmethylcellulose

(Methocel® K 100 M-Colorcon)	12.084 kg
Hydrogenated castor oil (Cutina® HR - Henkel)	1.976 kg
Ethylcellulose (Ethocel® standard 20 - Dow Chem.)	0.760 kg
Yellow iron oxide pigment (Sicopharm® - Gelb 10 - BASF)	0.152 kg
Colloidal silica (Syloid® 244 - Grace)	0.076 kg
Magnesium stearate (USP grade - Carlo Erba)	0.152 kg

The hydroxypropylmethylcellulose, hydrogenated castor oil and yellow iron oxide pigment were mixed in a suitable mixer and the mixture obtained was wetted with a solution of ethylcellulose in ethanol (7.6 litres of a 10% solution). The mass was then forced through an 800 micron grid, and after drying in an air circulation oven to constant weight the granulate obtained was passed through a 420 micron grid, the magnesium stearate and colloidal silica added and the system mixed for 20 minutes to obtain an easily flowable homogeneous mixture of yellow brown colour and defined as the granulate B1.

c - Preparation of tablets with applied support

c1 - Tablets with support applied to one face (see Figure 1):

To prepare the tablets a layer press (Manesty, Liverpool) able to produce multi-layer tablets was used. In this specific case the machine was adjusted to produce two-layer tablets, ie a layer containing the core and a second layer consisting of the support. The machine was fitted with circular dies of 7.0 mm diameter and

R

flat punches. The first loading hopper was filled with the granulate A1 (core), the chamber depth being adjusted to contain 96.0 mg of granulate, equivalent to 45 mg of active principle. The second loading hopper was filled with the granulate B1 (support) and the machine adjusted to deliver 38 mg of granulate, this quantity being sufficient to form on said core a continuous layer of about 0.5-0.8 mm thickness after compression.

The working pressure was adjusted to about 2500-3000 kg/cm^2. This procedure resulted in two-layer tablets consisting of a white layer (core) containing the active principle and a yellow-brown layer (support).

The tablet production was continuous at an hourly production rate of about 45-50,000 tablets.

c2 - Tablets with support applied to two faces (see Figure 2):

To prepare tablets comprising a core with two faces covered by the support the previously described press (Manesty layer press) was used, adjusted to form three-layer tablets. As in the previous case the machine was fitted with flat cylindrical punches of 7.00 mm diameter.

The first and third loading hopper were filled with said granulate B1 (support) whereas the second hopper was filled with the granulate A1 (core). The machine was adjusted to deliver 38 mg of granulate B1 in each of stations 1 and 3, and 96 mg of granulate A1 (equivalent to 45 mg of active principle) in station 2.

Operating in accordance with the known art and adjusting the compression force to about 3000 kg/cm^2, three-layer tablets were produced consisting of two yellow-brown layers (support) and an

intermediate white layer (core) as shown in Figure 2.

The tablet production was continuous with an hourly production rate of 35-40,000 tablets.

Tests to determine the "in vitro" release of the active substance from the tablets prepared in Example 1

The "in vitro" release tests were conducted on the tablets complete with support as obtained by the procedure described in Example 1. For comparison purposes identical control tests were conducted on tablets consisting of cores equal to those of Example 1 but with impermeable insoluble supports obtained by partial film coating using the method of US patent 4,839,177.

To better evaluate the influence of the support on the release kinetics of the active principle control tests were also carried out on the release from cores without supports.

The dissolution apparatus of USP XXI was used for the tests (paddle at 100 rpm) with 900 ml of distilled water at 37°C as the dissolution fluid.

The results given below represent the mean of six repeat tests.

- Release of diltiazem from the core without support (for comparison):

Time (min)	total fraction released
30	0.27
60	0.39
120	0.57
180	0.72
240	0.83
360	0.86

- Release of diltiazem from the tablet comprising an impermeable insoluble support applied by partial film coating (manual) on a single face (for comparison):

Time (min)	total fraction released
30	0.22
60	0.34
120	0.51
180	0.66
240	0.77
360	0.94

At the end of the test the support shows cracking and flaking.

- Release of diltiazem from the tablet comprising a support applied to one face by compression (Example 1 -C_1):

Time (min)	total fraction released
30	0.21
60	0.33
120	0.50
180	0.64
240	0.75

At the end of the test the support is unimpaired.

- Release of diltiazem from the tablet comprising an impermeable insoluble support applied by partial film coating (manual) on two faces (for comparison):

Time (min)	total fraction released
60	0.25
120	0.41
180	0.56
240	0.68
300	0.78
360	0.86

At the end of the test the support shows cracking and flaking.

- Release of diltiazem from the tablet comprising a support applied to two faces by compression (Example 1 -C_2):

Time (min)	total fraction released
60	0.21
120	0.39
180	0.53
240	0.66
300	0.76
360	0.85

At the end of the test the support is unimpaired.

EXAMPLE 2

a - Preparation of the core granulate

The following materials were used in the indicated quantities to prepare 25,000 cores:

Diltiazem (Fermion)	4.500 kg
Hydroxypropylmethylcellulose (Methocel K 100 M-Colorcon)	0.960 kg
Mannitol (USP grade - Carlo Erba)	3.450 kg
Ethylcellulose	

(Ethocel standard 20 - Dow Chem.)	0.450 kg
Magnesium stearate	0.100 kg
Colloidal silica (Syloid 244 - Grace)	0.100 kg
95° ethanol	7.500 litres

The diltiazem was mixed intimately with the mannitol and hydroxypropylcellulose in a suitable mixer. A solution of ethylcellulose in 95° ethanol was prepared separately and used to wet the previously formed powder mixture. The homogeneous mass obtained in this manner was forced through an 800 micron grid and then dried to obtain a granulate which was passed through a 420 micron grid. The granulate obtained was mixed with the magnesium stearate and the colloidal silica in a suitable mixer, to obtain the granulate A2, which was white in colour.

b - Preparation of the support granulate

For forming 100,000 supports a granulate of the following composition was prepared:

Hydroxypropylmethylcellulose (Methocel K 100 M-Colorcon)	11.92 kg
Hydrogenated castor oil (Cutina HR - Henkel)	1.95 kg
Ethylcellulose (Ethocel standard 20 - Dow Chem.)	0.75 kg
Yellow iron oxide pigment (Sicopharm - Gelb 10 - BASF)	0.150 kg
Colloidal silica (Syloid 244 - Grace)	0.075 kg
Magnesium stearate (USP grade - Carlo Erba)	0.150 kg
Ethanol	7.50 litres

The hydroxypropylmethylcellulose, hydrogenated castor oil and yellow iron oxide pigment were mixed in a suitable mixer and the mixture obtained was wetted with a solution of ethylcellulose in ethanol (7.5 litres of a 10% solution). The mass was then forced through an 800 micron grid, and after drying in an air circulation oven to constant weight the granulate obtained was passed through a 420 micron grid, the magnesium stearate and colloidal silica added and the system mixed for 20 minutes to obtain an easily flowable homogeneous mixture defined as the granulate B2 of yellow-brown colour.

c - Preparation of tablets with applied support

c_1 - Tablets with support applied to one face (see Figure 1):

To prepare the tablets a layer press (Manesty, Liverpool) able to produce multi-layer tablets was used. In this specific case the machine was adjusted to produce two-layer tablets, ie a layer containing the core and a second layer consisting of the support. The machine was fitted with circular dies of 11.0 mm diameter and flat punches. The first loading hopper was filled with the granulate A2 (core), the chamber depth being adjusted to contain 384 mg of granulate (equivalent to 180 mg of active principle). The second loading hopper was filled with the granulate B2 (support) and the machine adjusted to deliver 75 mg of granulate, this quantity being sufficient to form on said core a continuous layer of about 1 mm thickness after compression.

The working pressure was adjusted to about 2500-3000 kg/cm^2. This procedure resulted in two-layer tablets consisting of a white layer (core) containing the active principle and a yellow-brown layer

(support).

The tablet production was continuous at an hourly production rate of about 45-50,000 tablets.

c_2 - Tablets with support applied to two faces (see Figure 2):

To prepare tablets comprising a core with two faces covered by the support the previously described press (Manesty layer press) was used, adjusted to form three-layer tablets. As in the previous case the machine was fitted with flat cylindrical punches of 11.0 mm diameter.

The first and third loading hopper were filled with said granulate B2 (support) whereas the second hopper was filled with the granulate A2 (core). The machine was adjusted to deliver 75 mg of granulate B2 in each of stations 1 and 3, and 384 mg of granulate A2 (equivalent to 180 mg of active principle) in station 2.

Operating in accordance with the known art and adjusting the compression force to about 3000 kg/cm^2, three-layer tablets were produced consisting of two yellow-brown layers (support) and an intermediate white layer (core) as shown in Figure 2.

The tablet production was continuous with an hourly production rate of 30-35,000 tablets.

Tests to determine the "in vitro" release of the active substance from the tablets prepared in Example 2

The "in vitro" release tests were conducted on the tablets complete with support as obtained by the procedure described in Example 2.

To better evaluate the influence of the support on the release kinetics of the active principle, control tests were also carried out on the release from cores formed from granulate A2 and having

an identical composition and thus an equal diltiazem content (180 mg) and with the same geometrical form (11.0 mm diameter) but without a support.

The dissolution apparatus of USP XXI was used for the tests (paddle at 100 rpm) with 900 ml of distilled water at 37°C as the dissolution fluid.

The results given below represent the mean of six repeat tests.

- Release of diltiazem from the core without support (for comparison):

Time (min)	total fraction released
30	0.18
60	0.32
120	0.51
180	0.65
240	0.80

- Release of diltiazem from the tablet comprising a support applied to one face:

Time (min)	total fraction released
30	0.13
60	0.20
120	0.32
180	0.39
240	0.43
360	0.57
480	0.70
600	0.82

- Release of diltiazem from the tablet comprising a support applied to two faces:

colloidal silica in a suitable mixer, to obtain the granulate A3, which was white in colour.

b - Preparation of the support granulate

For forming 200,000 supports a granulate of the following composition was prepared:

Hydroxypropylmethylcellulose (Methocel® K 100 M-Colorcon)	12.000 kg
Hydrogenated castor oil (Cutina® HR - Henkel)	3.200 kg
Polyvinylpyrrolidone (USP grade - Prodotti Gianni, Milan)	0.760 kg
Yellow FCF aluminium lake (Colorcon®, Orpington UK)	0.152 kg
Colloidal silica (Syloid® 244 - Grace)	0.076 kg
Magnesium stearate (USP grade - Carlo Erba)	0.152 kg
95° ethanol	6.500 litres

The hydroxypropylmethylcellulose, hydrogenated castor oil and dye were mixed in a suitable mixer and the mixture obtained was wetted with a solution of polyvinylpyrrolidone in ethanol. The mass was then forced through an 800 micron grid, and after drying in an air circulation oven to constant weight the granulate obtained was passed through a 420 micron grid, the magnesium stearate and colloidal silica added and the system mixed for 20 minutes to obtain an easily flowable homogeneous mixture of yellow-brown colour and defined as the granulate B3.

c - Preparation of tablets with applied support

B

c1 - Tablets with support applied to one face (see Figure 1):

To prepare the tablets a layer press (Manesty, Liverpool) able to produce multi-layer tablets was used. In this specific case the machine was adjusted to produce two-layer tablets, ie a layer containing the core and a second layer consisting of the support. The machine was fitted with circular dies of 7.0 mm diameter and flat punches. The first loading hopper was filled with the granulate A3 (core), the chamber depth being adjusted to contain 95.25 mg of granulate (equivalent to 40 mg of Verapamil hydrochloride).

The second loading hopper was filled with the granulate B3 (support) and the machine adjusted to deliver 40 mg of granulate, this quantity being sufficient to form on said core a continuous layer of about 1 mm thickness after compression.

The working pressure was adjusted to about 2500-3000 kg/cm^2. Two-layer tablets were obtained consisting of a white layer (core) containing the active principle and a yellow-brown layer (support). The tablet production was continuous at an hourly production rate of about 45,000-50,000 tablets.

c2 - Tablets with support applied to two faces (see Figure 2):

To prepare tablets comprising a core with two faces covered by the support the previously described press (Manesty layer press) was used, adjusted to form three-layer tablets. As in the previous case the machine was fitted with flat cylindrical punches of 7.00 mm diameter.

The first and third loading hopper were filled with said granulate B3 (support) whereas the second hopper was filled with the

granulate A3 (core). The machine was adjusted to deliver 40 mg of granulate B3 in each of stations 1 and 3, and 95.25 mg of granulate A3 (equivalent to 40 mg of verapamil hydrochloride) in station 2.

Operating in accordance with the known art and adjusting the compression force to about 3000 kg/cm^2, three-layer tablets were produced consisting of two yellow-brown layers (support) and an intermediate white layer (core).

The tablet production was continuous with an hourly production rate of 35-40,000 tablets.

Tests to determine the "in vitro" release of the active substance from the tablets prepared in Example 3

The "in vitro" release tests were conducted on the tablets complete with support as obtained by the procedure described in Example 3.

For comparison purposes identical control tests were conducted on tablets containing an identical quantity of active principle but with the support obtained by partial film coating using the method of US patent 4,839,177.

To better evaluate the influence of the support on the release kinetics of the active principle, control tests were also carried out on the release from cores having an identical composition, the same geometrical form and containing the same quantity of Verapamil hydrochloride, but without supports.

The dissolution apparatus of USP XXI was used for the tests (paddle at 100 rpm) with 1000 ml of distilled water at 37°C as the dissolution fluid.

For the tests, three identical tablets prepared as described were inserted in known manner into a hard gelatin capsule (type Coni-

Supro Capsugel), each final pharmaceutical form thus containing 120 mg of Verapamil hydrochloride.

The results given below represent the mean of six repeat tests.

- Release of Verapamil HCl from cores without support (for comparison):

Time (min)	total fraction released
30	0.13
60	0.19
120	0.38
180	0.53
240	0.63
300	0.72

- Release of Verapamil HCl from tablets comprising an impermeable water-insoluble support applied by partial film coating on one face (for comparison):

Time (min)	total fraction released
30	0.07
60	0.12
120	0.21
180	0.28
240	0.37
360	0.50
480	0.62

- Release of Verapamil HCl from tablets comprising a permeable hydrophilic support applied to one face in accordance with the procedures of the present invention:

Time (min)	total fraction released
30	0.07
60	0.13
120	0.20
180	0.29
240	0.39
360	0.53
480	0.68

- Release of Verapamil HCl from the table comprising an impermeable insoluble support applied by partial film coating on two faces (for comparison):

Time (min)	total fraction released
60	0.07
120	0.12
180	0.18
240	0.24
360	0.37
480	0.45
600	0.58

- Release of Verapamil HCl from the table comprising a permeable hydrophilic support applied to two faces by compression in accordance with the procedures of the present invention:

Time (min)	total fraction released
60	0.07
120	0.13
180	0.19
240	0.26
360	0.38
480	0.48
600	0.62

EXAMPLE 4

Preparation of tablets with the support applied to the entire surface with the exception of one face in accordance with Figure 3.

The tablets were prepared using a Manesty Drycota machine (Manesty, Liverpool) consisting of two rotary presses connected together via a transfer system. In this machine the first press produces the cores, the transfer system allowing the cores to be continuously withdrawn and positioned on the surface of the lower punches of the second rotary press, exactly centered with respect to the dies. This second press is used to apply the support by compression.

In this specific case the first press was fitted with flat circular punches and dies of 10.0 mm diameter, the loading hopper was filled with granulate A1 obtained as in Example 1 and the depth of the filling chamber was adjusted so that it contained 256 mg of granulate A1, corresponding to 120 mg of active principle. Thus cores of 10.0 mm diameter and an average weight of 256 mg were obtained from the first press. The working pressure was adjusted to about 1500-2000 kg/cm^2.

The second press was fitted with flat circular punches and dies of

13.0 mm diameter. The filling hopper of the second press was filled with the granulate B1 obtained as in Example 1 and forming the support, the press being adjusted to deliver 180 mg of granulate. As the transfer system enabled the 10.0 mm cores to be positioned centrally on the lower punches and in the dies of the second press before the granulate was loaded, the indicated quantity (180 mg) of granulate B1 became distributed all around the core (within a circular ring of 1.5 mm thickness) and on the upper face, the lower face of the core being in contact with the punch surface.

Regular and correct operation of the system by which the cores are transferred from the first to the second press is essential in obtaining finished tablets in which that core face not covered is exactly centered, resulting in a regular lateral support layer of uniform thickness.

The working pressure of the second press was adjusted to about 2500-3500 kg/cm^2.

By this procedure the cores were covered by compression on their entire surface with the exception of one face. The finished tablets had one white face (core) containing the active principle and a yellow-brown coating (support) covering the entire core with the exception of one face.

The tablets were produced continuously at an hourly production rate of about 10-12,000 finished tablets.

Tests to determine the "in vitro" release of the active substance from the tablets prepared in Example 4

The "in vitro" release tests were conducted on the tablets complete

with support as obtained by the procedure described in Example 4. For comparison purposes analogous control tests were conducted on tablets consisting of cores equal to those of Example 4 and with impermeable insoluble supports obtained by partial film coating using the method of US patent 4,839,177.

To better evaluate the influence of the support on the release kinetics of the active principle control tests were also carried out on the release from cores without supports.

The dissolution apparatus of USP XXI was used for the tests (basket at 100 rpm) with 900 ml of distilled water at 37°C as the dissolution fluid.

The results given below represent the mean of six repeat tests.

- Release of diltiazem from the core without support (for comparison):

Time (min)	total fraction released
30	0.15
60	0.23
120	0.37
180	0.48
240	0.58
480	0.85

- Release of diltiazem from the tablet comprising an impermeable insoluble support applied by partial film coating (manual) over the entire surface with the exception of one face (for comparison):

Time (min)	total fraction released
30	0.08
60	0.12
120	0.18
240	0.27
360	0.37
480	0.49
600	0.62
900	0.87

At the commencement of the dissolution test the core swells considerably, to push beyond the impermeable insoluble support; this results during the initial stage in a more rapid release of active substance than the system obtained by compression.

- Release of diltiazem from the tablet comprising a support applied by compression over the entire core surface with the exception of one face, in accordance with the procedures of Example 4:

Time (min)	total fraction released
30	0.06
60	0.09
120	0.14
240	0.25
360	0.34
480	0.45
600	0.56
900	0.82

During the entire release test the support follows the swelling of

the core in a regular and homogeneous manner, resulting in regular and constant release of the active substance. The release kinetics, which can be expressed by the equation:

$$y = 2.734 + 0.088x \quad (R = 1.00)$$

is a linear function of time (zero order kinetics)

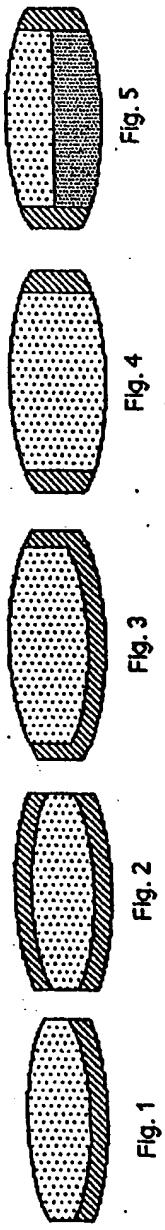


Fig. 5

Fig. 4

Fig. 3

Fig. 2

Fig. 1

Frank & Clark

P31220

Canada
Application by Assignee
Convention

The Petition of SmithKline Beecham PLC a British company, whose full post office address is: New Horizons Court, Brentford, Middlesex, TW8 9EP, UNITED KINGDOM.
sheweth:

1. That Graham Stanley LEONARD and David Philip ELDER whose full post office address is both: SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex, CM19 5AW, UNITED KINGDOM, both formerly at: SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY, UNITED KINGDOM, made the invention entitled:

   PAROXETINE CONTROLLED RELEASE COMPOSITIONS

which is described and claimed in the specification submitted herewith.

2. That the entire right to obtain a patent for the said invention has been assigned to your Petitioner.

3. That your Petitioner verily believes that it is entitled to a patent for the said invention having regard to the provisions of The Patent Act.

4. That your Petitioner requests that this application be treated as entitled to the rights accorded by Section 29 of the said Act having regard to the application of which particulars are set out below, and represents that the said application is/are the first application(s) for patent for the said invention filed in any country which by treaty, convention or law affords similar rights to citizens of Canada by it or anyone claiming under it.

   U.K. Patent Application No. GB 9514842.5. filed 20th July 1995.

5. That your Petitioner hereby nominates Gowling, Strathy & Henderson, Box 466, Terminal A, Ottawa KIN 8S3, Canada, to be its representatives for all purposes of the said Act, including the service of any proceedings taken thereunder.

6. That your Petitioner hereby appoints the said Gowling, Strathy & Henderson, as its agents, to sign the petition and drawings, to amend the specification and drawings, to prosecute the application, and to receive the patent granted on the said application; and ratifiesany act done by the said appointees in respect of the said application.

7. That your Petitioner therefore prays that a patent may be granted to it for the said invention.

Signed at : Brentford, Middlesex, UNITED KINGDOM, this day 27th January 1998

Peter John Giddings - Attorney

For SmithKline Beecham PLC

P31220

Canada
Assigment
Pending Application
Joint Inventors

In consideration of One ($l.00) dollar, and other good and valuable consideration paid to us by

SmithKline Beecham PLC

hereinafter called the Assignees, the receipt whereof is hereby acknowledged, we do hereby sell and assign unto the said Assignee,
all our right, title and interest in Canada and to our invention relating to:

PAROXETINE CONTROLLED RELEASE COMPOSITIONS

as fully described and claimed in the application for a patent for such invention and to all our corresponding right, title and
interest in and to any patent which may issue therefor.

Signed at:: this day of

Witness: _____ Inventor: _____
Graham Stanley LEONARD

Signed at this day of

Witness: _____ Inventor: _____
David Philip ELDER

WITNESS

I,
whose full post office address is

hereby declare that I was present and did see Graham Stanley LEONARD and David Philip ELDER sign this document before me today.

Date: _____ Signature of Witness: _____

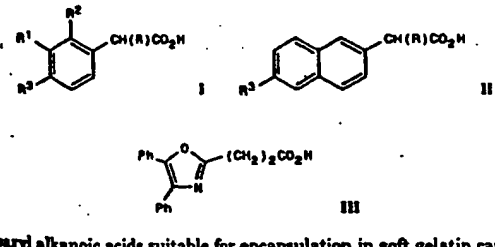
Gowling, Strathy & Henderson
Ottawa Canada

alginic acid; spacer = $NH(CH_2)_2NHCOCH_2NHCO(CH_2)_2CO$; degradable group =$(Ala)_2$—Pro—Val; drug = mafenide] was prepd. for therapeutic use.

124: 127141f Topically administrable compositions containing 3-benzoylphenylacetic acid derivatives for treatment of ophthalmic inflammatory disorders. Yanni, John M.; Graff, Gustav; Hellberg, Mark R. (Alcon Laboratories, Inc.) U.S. US 5,475,034 (Cl. 514—619; A61K31/165), 12 Dec 1995, Appl. 254,090, 6 Jun 1994; 10 pp. (Eng). Novel ester and amide derivs. of 3-benzoylphenylacetic acid are disclosed. The use of these compds. in topically administrable compns. for the treatment of ophthalmic inflammatory disorders is also disclosed. In vivo anti-inflammatory activity of 2-amino-3-benzoylbenzene acetic acid analogs was evaluated with rabbits; e.g. 2-amino-3-(4-chlorobenzoyl)-phenylacetamide effectively inhibited trauma-induced PGE_2 and plasma protein influx into the aq. humor in vivo. Ophthalmic formulations contg. the active ingredients were also provided.

124: 127142g Medicated wipe containing melanin formation-inducing substance for treatment of psoriasis. Goodman, Michael (Bioglan Laboratories Ltd.) PCT Int. Appl. WO 95 31,189 (Cl. A61K9/70), 23 Nov 1995, GB Appl. 94/9,945, 17 May 1994; 27 pp. (Eng). A wipe, comprising an absorbent woven or nonwoven fabric, cloth, or tissue substrate, impregnated with a pharmaceutically active agent which stimulates melanocytes to produce melanin, is effective in topical treatment of a skin condition, e.g. psoriasis, in combination with electromagnetic radiation in the range 220—700 nm. The wipe may also contain a nonvicous, lipophilic, UV-transparent emollient. The active agent may be e.g. 6- or 8-methoxypsoralen, trimethylpsoralen, 3-carbethoxypsoralen, cis- or trans-urocanic acid, or an amino oxo aliph. carboxylic acid such as δ-aminolevulinic acid. Application of the active agent with a wipe is safer than by spraying. Thus, 8-methoxypsoralen (0.0125—0.1 wt.%) was added to a mixt. of coconut oil 100, iso-Pr isostearate 100, and cyclomethicone 100 g, and 4-mL aliquots were deposited on cotton wipes which were sealed into pouches. After applying a thin coating of this mixt. from the wipe onto the skin of psoriasis patients, the skin was exposed to UV-A radiation for 2—5 min 2—3 times/wk for 4—8 wk. For compns. contg. δ-aminolevulinic acid, the radiation exposure is to visible light.

124: 127143h Solutions of aryl or heteroaryl substituted alkanoic acids in lipophilic solvents and soft gelatin capsules containing such solutions. Shelley, Rickey S.; Wei, Youching (R. P. Scherer International Corp.) PCT Int. Appl. WO 95 31,979 (Cl. A61K31/19), 30 Nov 1995, US Appl. 247,028, 19 May 1994; 34 pp. (Eng). Methods and compns. are disclosed for prepg. liq. mixts. of aryl or heteroaryl alkanoic acids suitable for encapsulation in soft gelatin capsules. The compns. comprise alkanoic acids of formulas I, II, and III (R = H, C_{1-6} alkyl; R^1 = H, halogen, C_{1-6} alkyl, phenylalkyl; R^2 = H, OH, C_{1-6} alkoxy; R^3 = H, C_{1-6} alkyl, Ph) or pharmaceutically acceptable salts thereof, and an effective solubilizing amt. of at least one lipophilic solvent, e.g. propanetriol triacetate. Ketoprofen (25 mg) was added to a homogeneous mixt. of propylene glycol dicaprilate/dicaprate 112 mg, 1,2,3-propanetriol acetate 72 mg, and polyoxyethylene (20) sorbitan monooleate 14 mg and mixt. was heated to 110—125° until ketoprofen was dissolved. After cooling and deaeration, the ketoprofen soln. can be encapsulated in soft gel capsules.



I

II

III

124: 127144j Oral pharmaceutical controlled-release liquid suspension containing oils and polymers and antioxidants. Modi, Pankaj Can. Pat. Appl. CA 2,143,070 (Cl. A61K47/30), 23 Aug 1995, US Appl. 199,933, 22 Feb 1994; 18 pp. (Eng). A controlled-release oral formulation for use with a variety of drugs, e.g. anti-Parkinsonian, cardiovascular and anti-epileptic drugs are formed in liq. suspension form. The ingredients in the suspension are water, and edible oil and a stabilizer for the liq. suspension, at least one pharmaceutically active ingredient, at least two water sol. biodegradable polymers, and optionally with at least one antioxidant to prevent degrdn. and oxidn. of the pharmaceutically active ingredients. A typical tsp dose of anti-Parkinson liq. suspension contains 15—150 mg carbidopa, 50—1500 mg levodopa, 100—800 mg of a combination of polyvinyl alc. and polysucrose, 10—50 mg oil, 5—15 mg antioxidant, e.g. vitamin E, 5—20 mg stabilizer, 10—15 mg colorants, 10—15 mg natural flavoring agents and 5 mL water.

124: 127145k Physiologically acceptable emulsions containing perfluorocarbon ether hydrides and methods of use. Moore, George G. L.; Flynn, Richard M.; Guerra, Miguel A. (Minnesota Mining and Mfg. Co.) PCT Int. Appl. WO 95 31,965 (Cl. A61K9/00), 30 Nov 1995, US Appl. 246,962, 20 May 1994; 59 pp. (Eng). This invention relates to physiol. acceptable emulsions of perfluorocarbon ether hydrides having 8—12 carbon atoms. These novel emulsions have various medical applications. They are esp. useful medically as contrast media for various biol. imaging modalities such as NMR. ^{19}F—magnetic resonance imaging, ultrasound, x-ray, and computed tomog., as oxygen transport agents or "artificial bloods" in the treatment of heart attack, stroke, and other vascular obstructions, as adjuvants to coronary angioplasty and in cancer redn. treatment and chemotherapy.

124: 127146m Topical antifungal preparations. Ijuin, Tomoko; Suzuki, Hiroyuki (Pola Kasei Kogyo K. K.) Jpn. Kokai Tokkyo Koho JP 07,277,975 [95,277,975] (Cl. A61K31/415), 24 Oct 1995, JP Appl. 94/18,780, 16 Feb 1994; 5 pp. (Japan). The prepns. contain ≥2 kinds of film-forming agents 1—5, H_2O 1—10, plasticizers 2.2—25, antifungal agents 0.1—5, and alcs. 60—95 wt.% and wt. ratio of the plasticizers to the film-forming agents is 2.2—5. The prepns. show high blocking effect on skin and antifungal agents penetrate into cornum effectively from the prepns. Et cellulose 3.5, methacrylic acid-Me methacrylate copolymer (I) 0.5, clotrimazole (II) 1, diphenhydramine 0.5, glycyrrhetinic acid 0.5, citric acid 0.1, H_2O 4, EtOH 80, and diisopropyl adipate (III) 9 wt.% were mixed to give a topical prepn. The prepn. spread over forearm was resistant to rubbing with wet gauze. Concns. of II in skin 9 and 24 h after application of the prepn. to the back skin of guinea pigs were 30 and 50 μg/site (circle with diam. 30 mm), resp., vs. 7 and 13 μg/site for a control prepn. contg. 11 wt.% III and no I.

124: 127147n Composition for treating gastrointestinal disorders. Winn, Gregory Murray; Borushek, John Benjamin (Hybrid Scientific Pty. Ltd.) PCT Int. Appl. WO 95 32,720 (Cl. A61K33/24), 7 Dec 1995, AU Appl. 94/5,968, 30 May 1994; 26 pp. (Eng). This invention relates to compns. and methods for the symptomatic treatment of gastrointestinal disease by pathogenic infection. The compn. comprises (1) a bismuth salt in an amt. effective for treating the gastrointestinal disorder and (2) Lactobacillus and/or Bifidobacterium. A capsule contg. Bi subcitrate 500 mg and freeze-dried Lactobaccillus acidophilus 750 mg was administered to volunteers for 3 times per day for 2wks; the capsule showed an anti-Helicobacter effect with few side effect.

124: 127148p Cyclosporin-containing composition and process for the preparation thereof. Kim, Hyun Soo; Choi, Jae Yoon; Lee, Hye Weon; Park, Young Keun; Choi, Sung Wook (Yuhan Corp.) PCT Int. Appl. WO 95 32,726 (Cl. A61K38/13), 7 Dec 1995, KR Appl. 9,412,288, 1 Jun 1994; 16 pp. (Eng). A compn. comprising 1.0—40 % of cyclosporin A, 0.1—30 % of an emulsifier, and 5—80 % of a porous dextrin, based on the total wt. of the compn., is claimed. The compn. has improved stability as well as a high dissoln. rate and blood concn. of cyclosporin. The compn. may preferably be administered orally. Cyclosporin A and Poloxamer 407 dissolved in ethanol and an aq. soln. of porous dextrin were mixed and the mixt. was spray-dried to give a powder, which was filled into capsules. The capsules were subjected to in vitro dissoln. tests and bioavailability tests with dogs.

124: 127149q Arteriosclerosis depressant. Tomioka, Hisao; Ohsawa, Hidefumi; Moroi, Masao; Kawashima, Toshio (Tokyo Tanabe Co., Ltd.) PCT Int. Appl. WO 95 32,714 (Cl. A61K31/435), 7 Dec 1995, JP Appl. 94/119,146, 31 May 1994; 12 pp. (Japan). This invention relates to 9-methyl-3-(1H-tetrazol-5-yl)-4-pyrido-[1,2-a]pyrimidin-4-one or a physiol. acceptable salt thereof, having an excellent activity of inhibiting growth of vascular smooth muscles, being efficacious against restenosis after PTCA treatment, and capable of treating or preventing diseases wherein the growth of vascular smooth muscles participate, such as arteriosclerosis. Antiarteriosclerotic tablets were formulated contg. 9-methyl-3-(1H-tetrazol-5-yl)-4-pyrido-[1,2-a]pyrimidin-4-one 10.0, lactose 56.0, corn starch 15.0, cryst. cellulose 15.0, hydroxypropyl cellulose 3.0, and magnesium stearate 1.0 wt.%.

124: 127150h Antitumor liposome preparations using alkylglyceryl oligomaltosides in lipid membranes. Endo, Masayuki; Miki, Toyohiko; Hatsutori, Takao (Pola Kasei Kogyo Kk) Jpn. Kokai Tokkyo Koho JP 07,285,886 [95,285,886] (Cl. A61K45/00), 31 Oct 1995, Appl. 94/76,855, 15 Apr 1994; 7 pp. (Japan). The liposome prepns. contain alkylglyceryl oligomaltosides in the lipid membrane and antitumor substances in the liposomes. The prepns. have long half-life in blood and show high tumor-targeting property. A liposome prepn. was prepd. from soybean lecithin 1.4, cholesterol 0.7, α,β-dipalmitylglyceryl maltotrioside (I) 1.4, propylene glycol 7, glycerin 7, PBS 82.5 wt.%, and neocarzinostatin ((II) 5455 unit/mL PBS. Half-life of the liposome prepn. after i.v. injection to a rabbit was 620 min, vs. 13 min for a control prepn. contg. no I. LD_{50} value of a liposome prepn. using α,α-dilauryglyceryl maltohexaoside in mice was 8120 unit II/kg, vs. 2000 unit/kg for the above control.

124: 127151j Compositions containing gastric mucin as gastric mucosa protectant to alleviate stomach irritation after oral administration of drugs. Ishiguro, Fumiko; Ishiguro, Junichi (Daikyo Yakuhin Kogyo Kk) Jpn. Kokai Tokkyo Koho JP 07,309,745 [95,309,745] (Cl. A61K9/08), 28 Nov 1995, Appl. 94/125,840, 17 May 1994; 5 pp. (Japan). Compns. for the alleviation of stomach irritation after oral administration of drugs contain gastric mucin as gastric mucosa protectant. Granules for alleviation of stomach irritation contained gastric mucin NNR 10, vitamin B_1 0.5, vitamin B_2 1.0, nicotinamide 5.0 mg, honey 2g, and flavors. The granules were dissolved in 100mL water prior to administration.

124: 127152k Use of water-soluble polysaccharides and corn starch in formulation of herb medicine extracts. Han, Itsuko; Ri, Renji; Cho, Kintoku; Hayashi, Funran (Ind Tech Res Inst) Jpn. Kokai Tokkyo Koho JP 07,309,768 [95,309,768] (Cl. A61K35/78), 28 Nov 1995, Appl. 94/103,064, 17 May 1994; 8 pp. (Japan). Water-sol. polysaccharides (e.g. guar gum and gum arabic) and corn starch are used in manufg. solid pharmaceutical dosage forms of herb medicine exts. Thus, siwutang ext. 9.75, corn starch 4.44, and carob gum 0.93 kg were mixed and made into moisture-resistant granules.